General

Guideline Title

Late (complicated) Parkinson's disease.

Bibliographic Source(s)

Oertel WH, Berardelli A, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira JJ, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schupbach M, Tolosa E, Trenkwalder C. Late (complicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 237-67. [332 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C, European Federation of Neurological Societies, Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the EFNS and the MDS-ES. Part II: late (complicated) Parkinson's disease. Eur J Neurol 2006 Nov;13(11):1186-202.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

Drug Withdrawal

- March 29, 2007 - WITHDRAWAL: Permax (pergolide) : Voluntary market withdrawal in the U.S. and worldwide due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.

Recommendations

Major Recommendations

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Point [GPP]) are defined at the end of the "Major Recommendations" field.

Symptomatic Control of Motor Complications

Motor Fluctuations

Wearing-off (end of dose akinesia, predictable ON-OFF)

- *Adjust levodopa dosing*. In an early phase, when motor fluctuations are just becoming apparent, adjustments in the frequency of levodopa dosing during the day, tending to achieve four to six daily doses, may attenuate the wearing-off (GPP).
- *Add catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase isoenzyme type B (MAO-B) inhibitors*. No recommendations can be made on which treatment should be chosen first – on average, all reduce OFF time by about 1 to 1.5 h/day. The only published direct comparison (Level A) showed no difference between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic, and is only recommended in patients failing on all other available medications (see the National Guideline Clearinghouse [NGC] summary of the European Federation of Neurological Societies [EFNS] guideline Early [Uncomplicated] Parkinson's Disease). Rasagiline should not be added to selegiline (Level C) because of cardiovascular safety issues.
- *Add dopamine agonists*. Non-ergot dopamine agonists are first-line compounds. Pergolide* and other ergot agonists are reserved for second-line treatment, due to their association with lung, retroperitoneal, and heart valve fibrosis. Oral dopamine agonists are efficacious in reducing OFF time in patients experiencing wearing-off. Currently, no dopamine agonist has proven better than another, but switching from one agonist to another can be helpful in some patients (Level B/C).
  *Note from the National Guideline Clearinghouse (NGC): On March 29, 2007, Permax (pergolide) was withdrawn from the market in the U.S. and worldwide due to safety concerns of an increased risk of cardiovascular events. See the U.S. Food and Drug Administration (FDA) Web site for more information.
- *Switch from standard levodopa to controlled release (CR) formulation*. CR formulations of levodopa can also improve wearing-off (Level C). This formulation is useful for the treatment of night-time akinesia (nocturnal end of dose akinesia) (GPP).
- *Add amantadine or an anticholinergic*. In patients with disabling recurrent OFF symptoms that fail to improve further with the above-mentioned strategies, the addition of an anticholinergic (in younger patients), or amantadine, may improve symptoms in some cases (GPP).

Severe Motor Fluctuations

If oral therapy fails to improve (marked to) severe predictable motor fluctuations, the following strategies can be recommended.

- *Deep brain stimulation (DBS) of the subthalamic nucleus (STN)* is effective against motor fluctuations and dyskinesia (Level A), but because of risk for adverse events the procedure is only recommended for patients below the age of 70 without major psychiatric problems or cognitive decline. Stimulation of other targets may also be effective, but results are less well documented.
- *Subcutaneous apomorphine* as penject (Level A) or pump (Level C).
- *Intrajejunal levodopa/carbidopa enteric gel* administered through percutaneous gastrostomy (PEG) can also help to stabilize patients with refractory motor fluctuations and dyskinesia (Level C).

Unpredictable ON-OFF

Deep brain stimulation of the STN is effective for unpredictable ON-OFF fluctuations (Level A). In the large studies of oral medical treatment for wearing-off, patients with unpredictable ON–OFF were either not included or constituted <5% of the total population. Therefore, insufficient evidence exists to conclude whether the results that are valid for wearing-off are also valid for unpredictable ON–OFF. There are only a few small studies specifically including patients suffering from unpredictable ON–OFF, although studies evaluating continuous dopaminergic stimulation also include patients suffering concomitantly from wearing-off and unpredictable ON–OFF. The same is true for concomitant dyskinesia, which frequently occurs during the ON phase of ON–OFF. Thus, there is insufficient evidence to conclude on specific strategies for ON–OFF, although the strategies described for dyskinesia and for wearing-off should be considered for unpredictable ON–OFF (GPP).

Unpredictable ON–OFF can have several components, one of which is delayed ON and, for which, oral dispersible levodopa formulations could have some value (Level C).

Note: By shortening the interval between levodopa doses to prevent wearing-off, and reducing the size of individual doses, the relation between the moment of intake of each dose and the subsequent motor effect can become difficult to disclose, especially when inadequate absorption also occurs. The resulting pattern of fluctuation and dyskinesia may falsely suggest unpredictable ON–OFF. In such patients, the actual mechanism of wearing-off and peak-dose dyskinesia may reappear by increasing the levodopa intake interval to about 4 h. However, in some patients, the

benefit may wane after weeks or months.

Dyskinesias

Peak-Dose Dyskinesia

- *Reduce individual levodopa dose size*, at the risk of increasing OFF time. The latter can be compensated for by increasing the number of daily doses of levodopa or increasing the doses of a dopamine agonist (Level C).
- *Discontinue or reduce dose of MAO-B inhibitors or COMT inhibitors* (GPP), at the risk of worsening wearing-off.
- *Add amantadine* (Level A) – most studies use 200 to 400 mg/day. The benefit may last <8 months. The use of other antiglutaminergic drugs is investigational. In some cases discontinuation of oral levodopa for a short period of time (3 days) with simultaneous continuous intravenous infusion of amantadine may temporarily improve dyskinesia (GPP).
- *Deep brain stimulation of the STN*, which allows reduction of dopaminergic treatment (Level A). Effective inhibition of severe dyskinesia may also be obtained by globus pallidus interna (GPi) stimulation (Level C).
- *Add atypical antipsychotics*, clozapine (Level C) (Pierelli et al., 1998; Durif, Debilly, & Galitzky, 2004) in dosages ranging between 12.5 and 75 mg/day up to 200 mg/day, or quetiapine (Level C) (Morgante et al., 2004; Katzenschlager et al., 2004). However, clozapine is associated with potential serious adverse events (agranulocytosis and myocarditis), which limits its use (GPP).
- *Apomorphine continuous subcutaneous infusion*, which allows reduction of levodopa therapy (Level C).
- *Intrajejunal levodopa infusion* in patients with marked peak dose dyskinesia and motor fluctuations (Level C).

Biphasic Dyskinesia

Biphasic dyskinesias can be very difficult to treat and have not been the subject of specific and adequate class I to III studies. Deep brain stimulation of the STN is effective (Level A), and the strategies described for peak-dose dyskinesias can also be considered for biphasic dyskinesia (GPP). Another option is increasing the size and frequency of levodopa dose, at the risk of inducing or increasing peak-dose dyskinesia. This latter strategy can be helpful, generally transiently, in those cases without peak-dose dyskinesia, or where they are considered less disabling than the biphasic type. A further option could be larger, less frequent doses, to give a more predictable response, which would better enable patients to plan daily activities (GPP). Finally apomorphine and intrajejunal levodopa infusion can be tried (Level C).

Off-Period and Early Morning Dystonias

- *Usual strategies for wearing-off* can be applied in cases of off-period dystonia (GPP).
- *Additional doses of levodopa or dopamine agonist therapy* at night may be effective for the control of dystonia appearing during the night or early in the morning (GPP).
- *DBS of the STN* (Level A) or GPi (Level C).
- *Botulinum toxin* can be employed in both off-period and early morning dystonia (GPP).

Freezing

Freezing, particularly freezing of gait, often occurs during the OFF phase and less frequently in both OFF and ON. The latter scenario often does not respond to dopaminergic strategies.

Options for OFF freezing are the same as those described for wearing-off. In addition, the use of visual or auditory cues is empirically useful for facilitating the start of the motor act once freezing has occurred (Level C).

In ON freezing, a reduction in dopaminergic therapy can be tried, although this may result in worsening of wearing-off.

Symptomatic Control of Non-motor Problems

Neuropsychiatric Complications

Treatment of Dementia in Parkinson's Disease (PD)

Most of the recommendations are off-label recommendations.

- *Discontinue potential aggravators*. Anticholinergics (Level B), amantadine (Level C), tricyclic antidepressants (Level C), tolterodine and oxybutynin (Level C) and benzodiazepines (Level C).
- *Add cholinesterase inhibitors*. Rivastigmine (Level A), donepezil (Level A), galantamine (Level C). Given the hepatotoxicity of tacrine, its use is not recommended (GPP). There may be idiosyncrasy in clinical response and side effects with these agents so it may be worth trying an alternative agent before abandoning (GPP).

- *Add or substitute with memantine* if cholinesterase inhibitors not tolerated or lacking efficacy (Level C).

Treatment of Psychosis in PD

- *Control triggering factors* (GPP). Treat infection and metabolic disorders, rectify fluid/electrolyte balance, treat sleep disorder.
- *Reduce polypharmacy* (GPP). Reduce/stop anticholinergic antidepressants, reduce/stop anxiolytics/sedatives.
- *Reduce antiparkinsonian drugs* (GPP). Stop anticholinergics, stop amantadine, reduce/stop dopamine agonists, reduce/stop MAO-B and COMT inhibitors, lastly, reduce levodopa. Stopping antiparkinsonian drugs can be at the cost of worsening motor symptoms. As a rule dopamine agonists have a higher psychosis-inducing potential than levodopa (GPP).
- *Add atypical antipsychotics*. Clozapine (Level A) – although it can be associated with serious haematological adverse events, requiring monitoring. There is insufficient data on quetiapine, but it is possibly useful (GPP). Quetiapine is thought to be relatively safe and does not require blood monitoring. Olanzapine (Level A), risperidone (Level C), and aripiprazole (GPP) are not recommended, and can induce – sometimes with a delay – parkinsonism (harmful).
- *Typical antipsychotics* (e.g., phenothiazines, butyrophenones) should not be used because they worsen parkinsonism.
- *Add cholinesterase inhibitors*. Rivastigmine (Level B), donepezil (Level C).

Treatment of Depression in PD

- *Optimize antiparkinsonian therapy* (GPP).
- *Tricyclic antidepressants* (Level B).
- *SSRIs* (GPP). SSRIs are less likely to produce adverse effects than tricyclic antidepressants (GPP).
- *'New' antidepressants – (mirtazapine, reboxetine, venlafaxine)*. No recommendation can be made.

Autonomic Dysfunction

Treatment of Orthostatic Hypotension in PD

General Measures

- *Avoid aggravating factors* such as large meals, alcohol, caffeine at night, exposure to a warm environment, volume depletion, and drugs known to cause orthostatic hypotension, such as diuretics or antihypertensive drugs, tricyclic antidepressants, nitrates, alpha-blockers used to treat urinary disturbances related to prostatic hypertrophy. Levodopa, dopamine agonists, and MAO-B inhibitors may also induce orthostatic hypotension.
- *Increase salt intake (1 g per meal)* in symptomatic orthostatic hypotension.
- *Head-up tilt of the bed at night (30°–40°)*, which may be helpful
- *Wear waist-high elastic stockings and/or abdominal binders*.
- *Exercise as tolerated*.
- *Introduce counter-manoeuvres to prolong the time for which the patient can be upright* (leg crossing, toe raising, thigh contraction, bending at the waist).
- *Highlight postprandial effects*. In some patients, hypotension occurs only postprandially. Warning the patient about this effect and taking frequent small meals may be helpful.

Drug Therapy

- *Add midodrine* (Level A).
- *Add fludrocortisone* (GPP: possibly effective, but note side-effects).

Treatment of Urinary Disturbance in PD

Most PD patients develop bladder problems. The symptoms include urgency, frequency, nocturia, and sometimes urge incontinence. The most common bladder disturbance is detrusor hyperactivity. Detrusor hypoactivity is uncommon, and usually caused by anticholinergic and tricyclic antidepressive drugs. Pronounced incontinence is relatively uncommon and when it occurs it mostly relates to late stage disease or akinesia. PD patients with bladder problems should be referred to a urologist, at least if response to anticholinergic therapy is insufficient or if incontinence is present. Further management includes the following:

- *When symptoms appear suddenly*: exclude urinary tract infection.
- *When frequency and polyuria dominate*: exclude diabetes mellitus.
- *Nocturia*: reduce intake of fluid after 6pm. Sleep with head-up tilt of bed to reduce urine production.
- *Night-time dopaminergic therapy* should be optimized (GPP). Apomorphine injections can be considered if outflow obstruction is the

dominating problem (GPP).

- *Use anticholinergic drugs* (GPP): drugs that do not pass the blood–brain barrier should have priority (since those that pass the blood–brain barrier tend to cause cognitive side effects in this patient category [GPP]). Substances: trospium chloride (10 to 20 mg two to three times per day), tolterodine (2 mg twice per day), oxybutynin (2.5 to 5 mg twice per day). Compared to other alternatives trospium is less apt to penetrate the blood–brain barrier. In case of cognitive side effects the advantage of better control of the urine must be balanced against the cognitive drawbacks. Postmicturation residual urine should be measured before and especially after start of anticholinergic therapy.
- A recent pilot study showed that botulinum toxin type A injected in the detrusor muscle under cystoscopic guidance ameliorated clinical symptoms and urodynamic variables in a small sample of PD patients with overactive bladder (Giannantoni et al., 2009).

Gastrointestinal Motility Problems

Dysphagia

Dysphagia difficulties in PD usually relate to disease severity and are rare in early PD. They are connected to a risk for asphyxia, aspiration pneumonia, malnutrition, and dehydration. There is a high risk of silent aspiration in PD. Pneumonia is a leading cause of death in later disease stages. The following recommendations can be given (GPP).

- Optimization of motor symptom control should be given priority. Levodopa and apomorphine can improve dysphagia at least in some patients.
- Early referral to speech therapist for assessment, swallowing advice, and further instrumental investigations if needed.
- Videofluoroscopy in selected cases to exclude silent aspiration.
- Enteral feeding options may need to be considered (short-term nasogastric tube feeding or longer- term feeding systems [percutaneous endoscopic gastrostomy]).

Concerning surgical therapies, rehabilitative treatments, and botulinum toxin therapies there is still very limited experience and these treatments cannot be generally recommended.

Gastric Dysfunction

- Gastric emptying is often delayed in PD, both in early and advanced patients. In addition to nausea and vomiting, symptoms may include early satiety, postprandial fullness, and abdominal pain. Through delayed absorption of medication motor fluctuations such as 'delayed on' can result. Domperidone can be considered to accelerate gastric emptying (GPP).
- Parenteral treatment such as transdermal patches can be considered for patients with severe fluctuations due to erratic gastric emptying (GPP). In cases with gastroparesis a percutaneous endoscopic gastrostomy (PEG) often becomes necessary.

Nausea and Vomiting

Domperidone (30 to 60 mg/daily) reduces dopaminergic drug-related gastrointestinal symptoms in patients with PD (Class II–IV) (Agid et al., 1979; Quinn et al., 1981; Day & Pruitt, 1989; Soykan et al., 1997). Ondansetron may be used as second-line drug. No other antiemetic is recommended. In fact, metoclopramide, cinnarizine, and prochlorperazine must be avoided (GPP) (see above).

Constipation

- Constipation is the most commonly reported gastrointestinal symptom in PD patients. It can occur in both clinical and preclinical stages of the disease and worsens with disease progression. Anticholinergic drugs can worsen constipation and should be removed (GPP).
- Among non-pharmacological therapies, increased intake of fluid and fibre are recommended (GPP).
- Increased physical activity can be beneficial (GPP).
- As medication polyethylene glycol solution (Macrogol) is recommended (Level A).
- Alternative treatments are fibre supplements such as psyllium (Level B) or methylcellulose and osmotic laxatives (e.g., lactulose) (GPP).
- Irritant laxatives should be reserved for selected patients and short treatment duration.

Treatment of Erectile Dysfunction in PD

Erectile dysfunction is more common in PD patients compared with age matched controls. Urological investigation should be considered. Comorbidities, such as endocrine abnormalities (e.g., hypothyroidism, hyperprolactinaemia, low testosterone) and depression should be considered and treated. Drugs associated with erectile dysfunction (e.g., alpha-blockers) or anorgasmia (e.g., SSRIs) should be discontinued. Dopaminergic therapy can have both negative and positive effects on this symptom. Sildenafil (50 to 100 mg, 1 h before sex) can be tried in PD patients with these problems (Level B). Other drugs of this class, like tadalafil (10 mg, 30 min to 12 h before sex) or vardenafil (10 mg, 1 h before

sex) can be alternative choices (GPP; no published experience in PD). In some patients apomorphine injections (5 to 10 min before sex) can also be an alternative treatment (GPP). Intracavernous injections of papaverine or alprostadil can be considered in selected patients (GPP; no published experience in PD).

Sleep Disorders

Treatment of Daytime Somnolence in PD

General Measures

- Assessment of nocturnal sleep disturbances (GPP)
- Optimize improvement of nocturnal sleep by reducing disturbing factors, such as akinesia, tremor, urinary frequency, etc. (GPP)
- Recommendation to stop driving (GPP)

Drug Therapy

- Decrease dose or discontinue sedative drugs prescribed for another medical condition (GPP).
- Decrease dose of dopaminergic drugs (mainly dopamine agonists; GPP). All dopaminergic drugs may induce daytime somnolence.
- Switch to other dopamine agonist (GPP).
- Add modafinil (Level B).
- Add other wake-promoting agents like methylphenidate (GPP).

Treatment of Sudden Onset Sleep in PD

There are no studies that specifically addressed the treatment or prevention of sudden-onset sleep in PD. Recommendations are similar to the ones proposed for excessive daytime somnolence (GPP).

Treatment of Rapid Eye Movement (REM) Sleep Behaviour Disorder (RBD) in PD

General Measures

- Protective measures to prevent sleep related injuries (safeguard bedroom environment) (GPP).
- Reduce or withdraw antidepressants, primarily SSRIs (GPP).

Drug Therapy

- Add clonazepam at bedtime (0.5 to 2 mg) (Level C).

Treatment of Sleep Problems in PD

- Add a bed-time intake of a standard or slow-release dose of levodopa (Level B).
- Transdermal rotigotine, pramipexole, and prolonged-release ropinirole improve sleep quality in advanced PD patients with motor fluctuations (Level A).
- Subthalamic nucleus deep brain stimulation improves sleep quality in advanced PD patients except for nocturnal motor phenomena of sleep disorders (Level B).

Definitions:

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point If the evidence is based on expert opinion and scientific evidence is lacking and therefore the rating of recommendation is below C, best practice is recommended (Good Practice Point).

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Parkinson's disease (PD)

Other Disease/Condition(s) Addressed

- Dementia
- Depression
- Incontinence
- Orthostatic hypotension
- Psychosis

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Geriatrics

Internal Medicine

Neurological Surgery

Neurology

Pharmacology

Psychiatry

Intended Users

Physicians

Guideline Objective(s)

To provide scientifically supported recommendations for the management of late (complicated) Parkinson's disease (PD)

Target Population

Patients with late (complicated) Parkinson's disease (PD)

Interventions and Practices Considered

Management of Motor Complications

Motor Fluctuations

1. Adjusting levodopa dosing
2. Switching from standard to controlled release (CR) formulation of levodopa
3. Adding catechol-O-methyltransferase (COMT) inhibitors, monoamine oxidase isoenzyme type B (MAO-B) inhibitors, dopamine agonists, amantadine, or an anticholinergic
4. Reduction or redistribution of total daily dietary proteins
5. Deep brain stimulation (DBS) of the subthalamic nucleus (STN)
6. Subcutaneous apomorphine as penjet or pump
7. Alternative delivery routes or alternative formulations of levodopa (e.g., intrajejunal levodopa/carbidopa enteric gel)

Dyskinesia

1. Reducing individual levodopa dose size
2. Discontinuing or reducing doses of MAO-B inhibitors or COMT inhibitors
3. Adding amantadine or atypical antipsychotics
4. DBS of the STN
5. Apomorphine continuous subcutaneous infusion
6. Intrajejunal levodopa infusion
7. Botulinum toxin (off period and early morning dystonia)
8. Additional doses of levodopa or dopamine agonist therapy at night (off period and early morning dystonia)

Management of Neuropsychiatric Complications

Dementia

1. Discontinuing potential aggravators
2. Adding cholinesterase inhibitors
3. Adding or substituting with memantine if cholinesterase inhibitors not tolerated or lacking efficacy

Psychosis

1. Controlling trigger factors
2. Reducing polypharmacy
3. Reducing antiparkinsonian drugs

4. Adding atypical antipsychotics or cholinesterase inhibitors

Depression

1. Optimizing antiparkinsonian therapy
2. Tricyclic antidepressants
3. Selective serotonin reuptake inhibitors (SSRIs)

Management of Autonomic Dysfunction

Orthostatic Hypotension

1. General measures such as avoiding aggravating factors, increasing salt intake, head-up tilt of the bed, elastic stockings, highlighting postprandial effects
2. Midodrine or fludrocortisone

Urinary Disturbance

1. General measures for treating urinary urgency and incontinence
2. Optimization of night-time dopaminergic therapy
3. Peripherally acting anticholinergics

Gastrointestinal Motility Problems

1. Levodopa and apomorphine to improve dysphagia
2. Early referral to speech therapist for dysphagia
3. Videofluoroscopy in selected cases of dysphagia
4. Enteral feeding options (short-term nasogastric tube feeding or longer-term feeding systems)
5. General measures for treating constipation (diet, laxatives) and nausea
6. Reducing or discontinuing drugs with anticholinergic activity
7. Adding domperidone

Erectile Dysfunction

Sildenafil or similar drugs

Daytime Somnolence

1. General measures for improving nocturnal sleep
2. Stopping driving
3. Decreasing dose or discontinuing sedative or dopaminergic drugs
4. Switching to other dopamine agonist
5. Adding modafinil
6. Adding other wake-promoting agents like methylphenidate

Note: Refer to the original guideline document for more details including information on medications that were considered but not recommended due to ineffectiveness, insufficient data, or serious adverse effects.

Major Outcomes Considered

Effectiveness of treatment in improving motor complications, neuropsychiatric complications, and autonomic dysfunction
Adverse effects of pharmacological and surgical interventions

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Searches were made in Medline, the full database of the Cochrane Library, and the International Network of Agencies for Health Technology Assessment (INAHTA). The databases were also searched for existing guidelines and management reports, and requests were made to European Federation of Neurological Societies (EFNS) for their National Guidelines. For the 2010 update, the Movement Disorder Society's Evidence Based Medicine Task Force conducted systematic checking of reference lists published in review articles and other clinical reports, and provided the results of a literature search for articles published until September 2009.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

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Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Classification of scientific evidence is made according to the European Federation of Neurological Societies (EFNS) guidance (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Classification of scientific evidence and the rating of recommendations are made according to the European Federation of Neurological Societies (EFNS) guidance (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). The original guideline focuses on the highest levels of evidence available. If the level of available evidence is only Level IV, i.e., if the evidence is based on the experience of the guidelines development group (expert opinion) and/or scientific evidence is lacking and therefore the rating of recommendation is below C, best practice is recommended (Good Practice Point [GPP]).

Meetings of the original author group were held in Chicago in June 2008 and in Paris in May 2009 to agree the strategy for revision of the original review, and additional members were invited to join the author group. Two authors were assigned to review the recent publications relating to each section of the original document, grade the evidence, and make any necessary revisions.

Rating Scheme for the Strength of the Recommendations

Rating of Recommendations

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Point If the evidence is based on expert opinion and scientific evidence is lacking and therefore the rating of recommendation is below C, best practice is recommended (Good Practice Point).

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see the "Availability of Companion Documents" field).

Evidence Supporting the Recommendations

References Supporting the Recommendations

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Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate treatment of late Parkinson's disease

Potential Harms

- *Monoamine oxidase isoenzyme type B (MAO-B) inhibitors*. Selegiline might increase or provoke dyskinesia in levodopa-treated patients, but this was not the primary outcome measure in the studies referred to. Rasagiline should not be added to selegiline because of cardiovascular safety issues.
- *Catechol-O-methyltransferase (COMT) inhibitors* should always be given with levodopa due to their mechanism of action. Tolcapone is potentially hepatotoxic (few fatal cases of liver injury have been reported), and is only recommended in patients failing on all other available medications.
- *Dopamine agonists*. When levodopa-treated patients with advanced Parkinson's disease receive a dopamine agonist to reduce OFF episodes, dyskinesia may occur or, if already present, worsen. In clinical practice, when an agonist is given as adjunct in patients with dyskinesias, the levodopa dose is usually reduced to minimize this problem. Nausea, headache, yawning and orthostatic hypotension are the

most common side-effects of apomorphine. Pergolide and other ergot agonists are reserved for second-line treatment, because of their association with lung, retroperitoneal, and heart valve fibrosis.

- *Clozapine* is associated with potential serious adverse events (agranulocytosis and myocarditis), which limits its use. Leucopenia is a rare (0.4%) but serious adverse event with clozapine, as is myocarditis. Consistently reported side-effects (even with low-dose clozapine) include sedation, dizziness, increased drooling, orthostatic hypotension, and weight gain.
- Increased tremor is an uncommon reason for discontinuation of *cholinesterase inhibitors*, while nausea and vomiting can also result in discontinuation of therapy in a minority of patients. These drugs may also be associated with a modest increase in risk for syncope, need for pacemaker insertion, and hip fracture. They may also worsen urinary frequency, urgency, and urge incontinence. Increased tremor is an uncommon reason for discontinuation of cholinesterase inhibitors.
- *Selective serotonin reuptake inhibitors (SSRIs)*. When added to dopaminergic therapy, SSRIs have the potential to induce a 'serotonin syndrome', which is a rare but serious adverse event.
- *Midodrine* is associated with supine hypertension, paresthesias, and goose bumps.
- *Fludrocortisone*. Hypertension, hypokalaemia and ankle oedema are the main side effects of fludrocortisone.
- *Peripherally acting anticholinergics* are associated with dry mouth, constipation, and cognitive adverse events.
- *Sildenafil*. Side-effects of this drug include a group of mild and transitory adverse reactions (headache, transient visual effects, flushing) and, occasionally, severe reactions (hypotension, priapism, cardiac arrest).
- *Clonazepam* may induce daytime sedation and exacerbate underlying obstructive breathing in sleep and increase the risk of nocturnal falling in the elderly.

Refer to the original guideline National Guideline Clearinghouse (NGC) summary of the European Federation of Neurological Societies (EFNS) Part I guideline Early (Uncomplicated) Parkinson's Disease for more information on adverse effects of these and other antiparkinsonian drugs.

- *Deep brain stimulation (DBS) of the subthalamic nucleus (STN)*. The severity of adverse events seldom warrants suspension of DBS. The occurrence of adverse effects related to the procedure, i.e., acute confusion, intracerebral bleeding, stroke, and seizures, or to device dysfunction, i.e. infection or stimulator repositioning, causing permanent severe morbidity or death, reaches up to about 4%. In a large observational study of more than 1,100 patients the mortality was found to be 0.4% and the permanent morbidity was 1%. However, most adverse effects are related to the treatment (either stimulatory or stimulatory in combination with pharmacological).
- *Unilateral pallidotomy*. Side effects with unilateral pallidotomy are generally limited, but the potential for severe complications due to haemorrhage or peri-operative complications is common to all stereotactic procedures. Symptomatic infarction was found in 3.9% of patients, and the mortality rate was 1.2%. Speech problems were found in 11.1% of patients and facial paresis in 8.4%. Neuropsychological functioning is usually unaffected, but frontal lobe functions and depression may show a modest deterioration.

See the original guideline document for a more detailed explanation of adverse effects of DBS of the STN and unilateral pallidotomy.

Contraindications

Contraindications

- Patients with abnormal liver function or a history of neuroleptic malignant syndrome, rhabdomyolysis or hyperthermia have to be excluded from taking tolcapone.
- Metoclopramide, cinnarizine, and prochlorperazine must be avoided.
- Typical antipsychotics (e.g., phenothiazines, butyrophenones) should not be used because they worsen parkinsonism.
- For recommendations concerning drug dosage, method and route of administration, and contraindications, the reader is referred to the local formulary or the manufacturer's instruction except when provided within the guideline recommendations.

Qualifying Statements

Qualifying Statements

- This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

- For recommendations concerning drug dosage, method and route of administration, and contraindications the reader is referred to the local formulary or manufacturer's instruction, except when provided within the guidelines' recommendation itself.
- The opinions and views expressed in the paper are those of the authors and not necessarily those of the Movement Disorder Society or the MDS Scientific Issues Committee (SIC).

Implementation of the Guideline

Description of Implementation Strategy

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Oertel WH, Berardelli A, Bloem BR, Bonuccelli U, Burn D, Deuschl G, Dietrichs E, Fabbrini G, Ferreira JJ, Friedman A, Kanovsky P, Kostic V, Nieuwboer A, Odin P, Poewe W, Rascol O, Sampaio C, Schupbach M, Tolosa E, Trenkwalder C. Late (complicated) Parkinson's disease. In: Gilhus NE, Barnes MP, Brainin M, editor(s). European handbook of neurological management. 2nd ed. Vol. 1. Oxford (UK): Wiley-Blackwell; 2011. p. 237-67. [332 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

European Academy of Neurology - Medical Specialty Society

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European Federation of Neurological Societies

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Guideline Committee

European Federation of Neurological Societies Task Force on Late (Complicated) Parkinson's Disease

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Financial Disclosures/Conflicts of Interest

A. Berardelli has received speaker honoraria from Allergan and Boehringer Ingelheim.

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GlaxoSmithKline, Medtronic, Merck-Serono, Neurosearch, Novartis, Orion Pharma, Schwarz-Pharma Neuroscience, Servier, Synosia, Teva, UCB, and Vifor Pharma.

W. Poewe has received honoraria for lecturing and advisory board membership from Novartis, GlaxoSmithKline, Teva, Boehringer Ingelheim, Schwarz, and Orion.

O. Rascol has received scientific grants and consulting fees from GlaxoSmithKline, Novartis, Boehringer Ingelheim, Eli Lilly, Teva Neuroscience, Eisai, Schering, Solvay, XenoPort, Oxford BioMedica, Movement Disorder Society, UCB, Lundbeck, Schwarz-Pharma, and Servier.

C. Sampaio has received departmental research grants from Novartis Portugal. Her department has also charged consultancy fees to Servier and Lundbeck, and she has received honoraria for lectures from Boehringer Ingelheim.

M. Schüpbach has received speaker's honoraria and travel reimbursement from Medtronic.

E. Tolosa has received honoraria for lectures from Boehringer Ingelheim, Novartis, UCB, GlaxoSmithKline, Solvay, Teva, and Lundbeck, and participated in advisory boards for Boehringer Ingelheim, Novartis, Teva, and Solvay.

C. Trenkwalder has received honoraria for lectures from Boehringer Ingelheim, UCB, Glaxo Pharmaceuticals, and AstraZeneca, and is member of advisory boards for Boehringer Ingelheim, UCB, Cephalon, Solvay, Novartis, and Teva/Lundbeck.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Horstink M, Tolosa E, Bonuccelli U, Deuschl G, Friedman A, Kanovsky P, Larsen JP, Lees A, Oertel W, Poewe W, Rascol O, Sampaio C, European Federation of Neurological Societies, Movement Disorder Society-European Section. Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the EFNS and the MDS-ES. Part II: late (complicated) Parkinson's disease. Eur J Neurol 2006 Nov;13(11):1186-202.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies (EFNS) Web site .

Availability of Companion Documents

The following is available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on April 12, 2007. The information was verified by the guideline developer on May 15, 2007. This summary was updated by ECRI Institute on November 6, 2007, following the updated U.S. Food and Drug Administration advisory on Viagra, Cialis, Levitra, and Revatio. This summary was updated by ECRI Institute on November 9, 2007, following the U.S. Food and Drug Administration advisory on Antidepressant drugs. This summary was updated by ECRI Institute on December 7, 2007, following the U.S. Food and Drug Administration advisory on Desmopressin Acetate. This summary was updated by ECRI Institute on July 25, 2008, following the U.S.

Food and Drug Administration advisory on Antipsychotics. This summary was updated by ECRI Institute on May 26, 2009, following the U.S. Food and Drug Administration advisory on Botox, Botox Cosmetic (Botulinum toxin Type A), and Myobloc (Botulinum toxin Type B). This summary was updated by ECRI Institute on August 17, 2009, following the updated FDA advisory on Botox and Botox Cosmetic (Botulinum toxin Type A), and Myobloc (Botulinum toxin Type B). This summary was updated by ECRI Institute on May 20, 2011 following the U.S. Food and Drug Administration advisory on antipsychotic drugs. This NGC summary was updated by ECRI Institute on February 20, 2012. This summary was updated by ECRI Institute on September 10, 2012 following the U.S. Food and Drug Administration advisory on Ondansetron (Zofran). This summary was updated by ECRI Institute on December 12, 2012 following the U.S. Food and Drug Administration advisory on Ondansetron (Zofran). This summary was updated by ECRI Institute on April 7, 2014 following the U.S. Food and Drug Administration advisory on Methylphenidate ADHD Medications. This summary was updated by ECRI Institute on October, 5 2015 following the U.S. Food and Drug Administration advisory on Clozapine.

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